

Response

Claims 25, 50, 77, and 102 have been canceled without prejudice or disclaimer. Claims 21, 46, 73, and 98 have been amended to delete reference to "immunogenic epitopes." Upon entry of the present amendment claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-101, 103-115, and 124 will be pending. No new matter has been added. Applicants reserve the right to pursue subject matter encompassed by all canceled claims in one or more divisional or continuation applications.

Claim Rejections - 35 U.S.C. §112

The Examiner has maintained and made final a rejection of claims 21-37, 46-63, 72-89, 98-115, and 124 under 35 U.S.C. § 112, alleging that the pending claims have not been sufficiently enabled by the present application. Applicants respectfully traverse and disagree. As an initial matter, this rejection is contradictory to the holding and principles set forth by the United States Supreme Court in *In Re Wands*. See, Reply filed by Applicants on July 3, 2002. The Examiner has alleged that the present situation is not analogous to *In Re Wands* because "the Colon Specific Protein of the instant application is not well characterized or well known in the art..." See, Paper No. 16, page 3, first full paragraph. This, however, is an irrelevant distinction. Whether or not a protein is "well characterized or well-known in the art" is immaterial to the production of antibodies. Indeed, such considerations were not a factor for the Supreme Court in *Wands*, nor are such considerations pertinent to the generation of antibodies by those of ordinary skill in the art. Production of antibodies specific for a given protein is quite easily accomplished by those of ordinary skill even though extremely little may be known about that protein. For example, antibodies specific for a given protein are routinely generated from sources such as partially purified protein extracts and even raw plasmid DNA (*i.e.*, without even having the protein in hand). Hence, institution of a requirement that proteins be "well characterized or well-known in the art" before a specification may be considered enabling of antibody production constitutes a rather arbitrary and capricious standard.

Furthermore, the Examiner has also maintained the present rejection by asserting that “neither the specification nor the art of record teaches how to use the claimed invention because no function can be ascertained for the Colon Specific Protein and therefore no function can be ascertained for an antibody which binds said antigen.” *See*, Paper No. 16, page 3, first full paragraph. As an initial matter, Applicants have previously explained that the presently claimed antibodies are useful for, *inter alia*, detecting and targeting colon cancer cells. The Examiner has not presented any countervailing evidence to rebut Applicant’s assertions of utility.¹ Second, rejecting the present antibody claims by alleging that “no function can be ascertained for the Colon Specific Protein and therefore no function can be ascertained for an antibody which binds said antigen” is inappropriate in view of the U.S. Patent previously issued with claims drawn to the Colon Specific Protein. *See*, U.S. Patent No. 6,080,722, issued June 27, 2000 (to which the present application claims priority). Hence, given that issued patents are, by law, presumptively valid and since it was previously determined (by the U.S. Patent Office) that the Colon Specific Protein has a function sufficient to justify issuance of a patent, it appears quite capricious and contradictory to now reject antibody claims by declaring that “no function can be ascertained for the Colon Specific Protein... [therefore] no function can be ascertained for an antibody which binds said antigen.” *See*, Paper No. 16, page 3, first full paragraph.

¹ In assessing the credibility of the asserted utilities, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, “question”) the truth of the statement of utility. *See*, M.P.E.P. § 2107 at 2100-30 and 2100-40; *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995); and, *In re Cortright*, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). Thus, the Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered “false” by a person of ordinary skill in the art. *See id.* Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, if applicants have presented reasoning used in asserting a utility, the Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Applicants’ assertion of utility. *See id.* For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

Additionally, it is also asserted in the pending rejection that “the specification teaches that the colon specific gene is found in all cells of the body...Thus, it appears that although Applicant names the newly discovered gene as a colon specific gene, it is not colon specific.” *See*, Paper No. 16, page 3. First, it is unclear which part of the specification the Examiner is referring to when making this statement. Second, of course the colon specific gene “is found in all cells of the body” because, except for a limited subset of cells (for example, enucleated cells (e.g. red blood cells), some differentiated cells with specifically rearranged genes (e.g. antibody producing B-cells), and germ cells (e.g. sperm and egg cells)), all genes are found in all cells of the body by virtue of each cell containing a complete human genome. Therefore, one of ordinary skill in the art would certainly understand that the colon specific gene can be found in (almost) all cells of the body. Thus Applicants point out that, in being one’s own lexicographer, “colon specific gene” and “colon specific protein” are simply convenient names by which to refer to the novel protein and polynucleotide sequences described in the present application. Furthermore, the pertinent issue is not presence or absence of a gene in a cell but, instead, is one of expression of that gene. Hence, the specification teaches that the colon specific gene is primarily, though not exclusively expressed in colon tissues. *See e.g.*, specification page 5, penultimate paragraph.

Additionally, the Examiner indicates “the specification teaches that the expression product is primarily limited to the colon in non-diseased individuals and then teaches that the colon specific gene is overexpressed in colon cancer...The two teachings are confusing because they appear to be contradictory.” *See*, Paper No. 16, page 3. Again, it is unclear exactly which part or parts of the specification the Examiner is referring to in making this statement. Applicants believe the Examiner may be referring to the specification at page 11, first paragraph, for which the following explanation is provided. The first paragraph on page 11 discusses the process of metastasis, wherein colon cancer cells (expressing the colon specific gene) may metastasize from the colon to other parts of the body. Hence, this paragraph indicates that “transcription of colon specific mRNA is primarily limited to the colon in non-diseased individuals” (in contrast to diseased individuals wherein the colon and cells in other parts of the body may express the colon specific gene because of the migration (metastasis) of cancerous colon cells to those body parts). Thus, the reference to expression

limited to colon in non-diseased individuals does not imply lack of expression in the colon of diseased individuals.

The Examiner also asserts that “the claim[s] are drawn to antibodies which bind to fragments or variants of SEQ ID NO:2 and it cannot be determined from the information in the specification or the art of record, what effects the impact of these variations would have on protein function, even if that function were known...Applicants arguments have not been found persuasive and the rejection is maintained.” *See*, Paper No. 16, page 4, first paragraph. Applicants strongly object. Despite Applicants’ previous reply addressing each of the issues raised by the Examiner, the Examiner has improperly chosen to maintain and make final a rejection without providing any evidence, reasoning, or explanation for so doing. Moreover, given that Applicants have already asserted that at least one use for the presently claimed antibodies is to provide colon cancer targeting molecules, it would be quite clear to one of ordinary skill in the art that antibodies that bind fragments and variants of SEQ ID NO:2 would also have utility as colon cancer targeting molecules.

Finally, the Examiner asserts that “it cannot be determined from the information in the specification or in the art whether or not the protein encoded by the RNA is overexpressed in colon cancer compared to normal control for the reasons of record or that the expressed protein can be used for diagnosis or treatment of colon cancer or any other type of cancer.” *See*, Paper No. 16, page 4. Applicants disagree. Again, despite Applicants’ previous reply and reasoning addressing each of the issues raised by the Examiner, the Examiner has improperly maintained and made final a rejection without providing evidence, reasoning, or explanation for so doing.

Surprisingly, the Examiner has disregarded a sworn Declaration submitted by an expert in the field most closely related to the presently claimed invention. Hence, the Examiner indicated “[t]he Declaration and the argument have been considered but have not been found persuasive because...there is no objective evidence demonstrating expression of the protein in colon cancer tissue compared to normal colon tissue.” *See*, Paper No. 16, page 4, last paragraph (emphasis added). The RNA and protein expression data submitted (and attested to by Dr. Adam Bell) in the previous reply most certainly constitutes objective evidence. The Examiner appears to have arbitrarily and capriciously decided to simply *not believe* the submitted data and Declaration. This is further evidenced by the Examiner’s

statement that "it is clear that Dr. Bell is not able to predict that the protein will be overexpressed in some human colon cancers..." *See*, Paper No. 16, pages 4-5. In contrast to this statement, however, Dr. Bell has predicted overexpression of the protein in human colon cancers. *See*, Declaration submitted July 3, 2002, page 2, item 7 (b).

Finally, the Examiner continues to assert, without citing any authority or supporting evidence, that mRNA expression is not generally predictive of protein expression. *See*, Paper No. 16, page 5, first paragraph. Instead, the Examiner has referred to a few exceptions to the general rule, and claimed that the exceptions disprove the rule. Moreover, Applicant's previously addressed the rationale first set forth by the Examiner in making this assertion, but the Examiner has failed to address both the arguments and authority cited by Applicant's in reply, which support Applicants' contention that, in most cases, mRNA expression is predictive of protein expression. *See e.g.*, Alberts et al. as cited on page 5 of reply submitted July 3, 2002. Hence, the Examiner has not met the required burden of submitting corroborating support for the position that mRNA expression is not usually predictive of protein expression.

The Examiner has stated that "Applicant is invited to present objective evidence from the literature demonstrating that those of skill most often look to mRNA expression levels as predictive of the relative protein expression levels." *See*, Paper No. 16, page 5. Applicants address this invitation first by pointing out that the Examiner, by excerpting a portion of a sentence from Applicants' previous response, has instituted an inappropriate standard in correlating mRNA with protein expression. Hence, in contrast to the wording used in the Examiner's invitation, the Applicants did not so broadly state that "those of skill most often look to mRNA expression levels as predictive of the relative protein expression levels." The Examiner's statement implies that those of skill in the art most preferably look to mRNA expression to determine protein expression. Instead, Applicants statement was "[W]hen investigating the expression levels of a new gene and protein those of skill most often look to mRNA expression levels as predictive of the relative protein expression levels." *See*, Reply filed July 3, 2002, page 5, second paragraph (emphasis added). Applicant's statement indicates that in first-tier characterization of a new gene and protein, investigators look to mRNA expression with an understanding that for most genes it is predictive of protein expression. In this regard, Applicants herewith submit copies of four publications disclosing

new genes and proteins wherein the investigators first looked to mRNA expression data to predict tissue specific protein expression levels. See, Exhibits 1-4 (Copies of publications by: Qu, et al., *J. Biol. Chem.*, vol. 277, no. 38, pp.35574-35585 (2002); Katsu, et al., *J. Biol. Chem.*, vol. 277, no. 46, pp.44220-44228 (2002); Sato, et al., *J. Biol. Chem.*, vol. 277, no. 40, pp.37678-37684 (2002); and, Uyama, et al., *J. Biol. Chem.* (in press), published online Nov. 13, 2002 as Manuscript No. M209446200 (29 pages). Applicants note that these four publications represent a small sample of recent articles from just one highly respected journal. At the Examiner's request Applicants can provide many more supporting publications.

In sum, Applicants have submitted: (1) a Declaration by an expert in the field; (2) a reference from a classic textbook in the field of molecular biology (often a required textbook in graduate level courses); and, (3) a sample of four recent publications, all of which support Applicant's assertion that those of ordinary skill in the art expect and understand that mRNA expression is usually predictive of protein expression. In contrast, the Examiner has presented only individual exceptions and no evidence reflecting on the general rule.

The Examiner has also maintained the pending rejection with certain inaccurate statements about the pending claims. As such, the Examiner has stated:

Applicant argues that the claims are drawn to antibodies which specifically bind to fragments of SEQ ID NO:2 and do not recite antibodies which bind to variants of SEQ ID NO:2. The argument has been considered but has not been found persuasive because the claims are drawn to antibodies produced by immunizing an animal with a protein selected from the group consisting of a "protein which comprises an immunogenic fragment" of the amino acid sequence of SEQ ID NO:2, 30 amino acids of SEQ ID NO:2, 50 amino acids of SEQ ID NO:2. A protein that comprises an immunogenic fragment of SEQ ID NO:2, 30, 50 amino acids, reads on a protein that comprises 4-6, 50, 30 contiguous amino acids of SEQ ID NO:2 and also hundreds of other amino acids. The claim does not state that the immunogenic fragment, 30, 50 amino acids are exposed on the surface. The claim does not even require that the antibody bind to SEQ ID NO:2. The claims as written are drawn to a highly variant group of proteins which are variants of SEQ ID NO:2.

See, Paper No. 16, pages 5-6 (emphasis added).

First, Applicant's disagree with the contention that "[a] protein that comprises an immunogenic fragment of SEQ ID NO:2...reads on a protein that comprises 4-6, 50, 30 contiguous amino acids of SEQ ID NO:2 and also hundreds of other amino acids." However,

for the sake of expediting prosecution, Applicants have herein amended pending claims 21, 46, 73, and 98 to delete references encompassing antibodies which bind "immunogenic fragments." Accordingly, the Examiner's rejection, in as much as it applies to antibodies that bind immunogenic fragments, has been rendered moot.

Second, it is incorrect that "[a] protein that comprises... 30 [or], 50 amino acids, reads on a protein that comprises 4-6, 50, 30 contiguous amino acids of SEQ ID NO:2 and also hundreds of other amino acids." Indeed, far from the "hundreds of other amino acids" the Examiner has not cited a single prior art protein with as few as 30 contiguous amino acids matching SEQ ID NO:2.

Third, it is unclear what the Examiner is requiring by stating that "The claim does not state that the immunogenic fragment, 30, 50 amino acids are exposed on the surface." However, whatever the intended meaning, a requirement that the claims state the amino acids be exposed on any surface would be inconsistent with settled case law and M.P.E.P. guidelines on the requirements for enablement of antibody claims.

Fourth, the statement that "The claim does not even require that the antibody bind to SEQ ID NO:2" is either incorrect or misapplied. This statement is incorrect because each and every claim that is not drawn to antibodies that bind polypeptides encoded by the ATCC Deposit does, in fact, recite that the claimed antibodies bind to some portion of SEQ ID NO:2. If the Examiner has found this not to be the case, it is respectfully requested that Applicants attention would be directed to the claim or claims in question. Further, this statement is misapplied because the claims which are drawn to antibodies that bind polypeptides encoded by the ATCC Deposit do not require that the antibody bind to SEQ ID NO:2 because these claims represent an independent means of claiming the present invention.

Fifth, the Examiner has indicated "The claims as written are drawn to a highly variant group of proteins which are variants of SEQ ID NO:2." This is incorrect because the present claims are drawn to antibodies not proteins (ignoring for ease of discussion the fact that antibodies are actually proteins). Therefore, the claims are not drawn to a highly variant group of proteins. The claims are drawn to antibodies that bind to either at least a portion of SEQ ID NO:2 or at least a portion of the polypeptide encoded by the ATCC Deposit. Hence, the claims are not drawn to "a highly variant group of proteins."

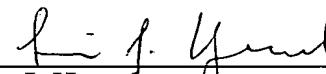
In view of the amendments and remarks made herein Applicants submit that each asserted rejection or objection has been accommodated, overcome, or rendered moot. Accordingly, Applicants request that the rejection of pending claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-101, 103-115, and 124 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks above be entered and made of record in the file history of the instant application.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Soppet, et al.

Application No.: 09/525,041

Group Art Unit: 1642

Filed: March 14, 2000

Examiner: Susan N. Ungar

For: Colon Specific Gene and Protein

Version With Markings To Show Changes Made
(underline = text inserted, strike-through = text deleted)

In the Claims

Claims 25, 50, 77, and 102 have been canceled without prejudice or disclaimer.

Claims claims 21, 46, 73, and 98 have been amended as shown below:

21. An isolated antibody or portion thereof that specifically binds to a protein selected from the group consisting of:

(a) a protein whose sequence consists of amino acid residues 2 to 158 of SEQ ID NO:2;

(b) ~~a protein whose sequence consists of an immunogenic fragment of the amino acid sequence of SEQ ID NO:2;~~

(c) a protein consisting of a fragment of SEQ ID NO:2, wherein said fragment comprises at least 30 contiguous amino acid residues of SEQ ID NO:2; and

(d) ~~(c)~~ a protein consisting of a fragment of SEQ ID NO:2, wherein said fragment comprises at least 50 contiguous amino acid residues of SEQ ID NO:2.

46. An isolated antibody or portion thereof produced by immunizing an animal with a protein selected from the group consisting of:

(a) a protein whose sequence comprises amino acid residues 2 to 158 of SEQ ID NO:2;

(b) a protein whose sequence comprises an immunogenic fragment of the amino acid sequence of SEQ ID NO:2

(e) a protein whose sequence comprises at least 30 contiguous amino acid residues of SEQ ID NO:2; and

(d) (c) a protein whose sequence comprises at least 50 contiguous amino acid residues of SEQ ID NO:2,

wherein said antibody or portion thereof specifically binds to the amino acid sequence of SEQ ID NO:2.

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73. An isolated antibody or portion thereof that specifically binds to a protein selected from the group consisting of:

(a) a protein whose sequence consists of the amino acid sequence of the mature polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129;

(b) a protein whose sequence consists of an immunogenic fragment of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129;

(e) a protein consisting of a fragment of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129, wherein said fragment comprises at least 30 contiguous amino acid residues of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129; and

(d) (c) a protein consisting of a fragment of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129, wherein said fragment comprises at least 50 contiguous amino acid residues of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129.

98. An isolated antibody or portion thereof produced by immunizing an animal with a protein selected from the group consisting of:

(a) a protein whose sequence comprises the amino acid sequence of the mature polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129;

(b) ~~a protein whose sequence comprises an immunogenic fragment of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129;~~

(c) a protein whose sequence comprises at least 30 contiguous amino acid residues of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129; and

(d) ~~(c)~~ a protein whose sequence comprises at least 50 contiguous amino acid residues of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129;

wherein said antibody or portion thereof specifically binds to the polypeptide encoded by the cDNA contained in ATCC Deposit Number 97129.

600